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Original Article

Sleep apnea increased incidence of primary central nervous system cancers: a nationwide cohort study

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ABSTRACT

Introduction: Obstructive sleep apnea (OSA) was associated with increased incidence of all cancers. We aimed to determine the risk for primary central nervous system (CNS) cancers in patients with sleep apnea syndrome.
Methods: A total of 23,055 incident cases of newly diagnosed sleep apnea syndrome (sleep apnea group) were identified between 2000 and 2003 in the medical claims database of Taiwan's National Health Institute (NHI) program and were matched by age and gender to patients without OSA (comparison group) in the same period. The occurrence of primary malignant CNS cancers was measured 2 years after the index date over a 10-year period.
Results: The incidence density of primary CNS cancers (per 10,000 individual-years) was 2.14 and 1.28, respectively, for the OSA and comparison groups. The overall risk for developing primary CNS cancers was significantly higher in the OSA group (adjusted hazard ratio [HR], 1.54; $P = 0.046$) after adjusting for age, gender, and obesity, among other variables. Subgroup analysis revealed a significantly higher risk for primary brain cancers but not primary spinal cord cancers in the OSA subgroup (adjusted HR, 1.71; $P = 0.027$). The analysis also revealed a significantly higher risk for primary CNS cancers in the insomnia with OSA subgroup (adjusted HR, 2.20; $P = 0.001$) and in the OSA without surgical treatment subgroup (adjusted HR, 1.831; $P = 0.003$).
Conclusions: OSA, especially with insomnia, may increase the risk for primary CNS cancer development, though surgical treatment may reduce this risk in participants with OSA.

1. Introduction

Patients with obstructive sleep apnea (OSA) and poor quality of sleep may be at increased risk for obesity, diabetes mellitus (DM), cardiovascular disease, cognitive impairment and total mortality [1,2]. OSA also may contribute to several organ system dysfunctions including auditory [3] and ophthalmic [4] degeneration, as well as overactive bladder [5]. However, little information is available regarding the association of OSA and tumor formation. Evidence shows that tumor hypoxia and its related molecular mediators regulate multiple steps of tumorigenesis, including tumor formation, progression, and response to therapy [6]. Hypoxia also plays a role in glioma tumorigenesis [7]. The progression of low-grade astrocytoma to glioblastoma multiforme may be mediated by hypoxia-induced phenotypic changes and subsequent clonal selection of cells that overexpress hypoxia-responsive molecules [7,8]. From these experimental observations, we hypothesized that OSA and subsequent tissue hypoxia might lead to cancer formation. However, this relationship in humans has not yet been firmly established.

A previous study showed that short duration of sleep increased the risk for colorectal adenoma [9]. It has been reported that an adequate night of sleep may reduce the risk for breast cancer [10,11]. Recently, OSA was associated with increased incidence of all cancers, especially in men and patients younger than the age of 65 years in a large multicenter Spanish cohort study [12]. Thus it seems that sleep apnea may increase the risk for malignant tumors at various sites. Because the central nervous system (CNS) is a high oxygen-demanding organ, it may be prone to hypoxia damage. Moreover, tissue hypoxia resulting from sleep

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apnea may increase the risk for cancer formation, but it remains unclear if OSA can increase the risk for primary CNS cancers in humans. Therefore, our study aimed to address this concern.

2. Materials and methods

2.1. Study design and data collection

Our study used data retrieved from the medical claims database of Taiwan's National Health Institute (NHI) program. In Taiwan, National Health Care is obligatory and individuals rarely are excluded from this system. Thus the NHI program covers more than 96% of the population in the country and has contracted with 97% of all hospitals and clinics in Taiwan [13]. The study protocol was approved by the Institutional Review Board of Dalin Tzu Chi Hospital. Further, this board waived the need for written inform consent, as the files of participants were delinked from the database.

In the period between January 2000 and December 2003, a cohort of 23,055 participants (ages, 20–50 years) with newly diagnosed sleep apnea (*The International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM] codes 780.51, 780.53 and 780.57) was identified as the sleep apnea group from the population of visitors to the outpatient departments of all hospitals and clinics in Taiwan between 2000 and 2003. Sleep apnea was diagnosed by polysomnography (PSG) showing an apnea-hypopnea index of greater than five events per hour. However, PSG was less available and less frequently performed in Taiwan in early 2000. Therefore, OSA was diagnosed by clinical symptoms (i.e., persistent snoring and apnea with witness). The date of the first diagnosis of OSA in the database between 2000 and 2003 was defined as the index date, and participants with OSA before the year 2000 were excluded to ensure that no study participant had OSA prior to the beginning of the study. In addition, we divided the OSA group into two subgroups: insomnia with sleep apnea (ICD-9-CM codes 780.57 and 785.51) subgroup and hypersomnia with sleep apnea (ICD-9-CM code 780.53) subgroup.

All participants with OSA were further divided into a surgical treatment group if they received surgical treatment for their OSA and a nonsurgical treatment group if they did not receive surgical treatment. The same database was used to randomly select the comparison group (patients without OSA in the same period). Participants in the comparison group were matched (1:3) by age within 2 years and gender to participants in the OSA group. Participants with other respiratory abnormalities (ICD-9-CM code 786.09), apnea (ICD-9-CM code 786.03), history of primary malignant CNS cancers (ICD-9-CM codes 191–192), or metastatic CNS cancers diagnosed before the index date and within 2 years after the index date were excluded.

2.2. Study end point

To avoid a possible reverse causal relationship between OSA and primary CNS cancers, new diagnosis of primary malignant CNS cancers (including brain cancers and spinal cord cancers) 2 years after the index date was defined as the end point in our study. However, the association of OSA with all cancers or other types of cancer was not tested. The observation period began on the index date, which was the same for both the sleep apnea group and the comparison group, and ended on the date of CNS cancer diagnosis or date of censoring before or on December 31, 2009. The length of follow-up was calculated for each patient diagnosed with primary CNS cancers. The completion date was defined as the date of death or the date of withdrawal from the NHI program.

2.3. Statistical analysis

The significance of the differences in age, gender and baseline comorbidities between the OSA group and the comparison group was assessed using t tests or χ^2 tests. The incidence of primary CNS cancers was estimated for the two groups. Cox proportional hazards regression models were used to assess the effects of OSA syndrome on primary CNS cancer risk after adjustment for age, gender and comorbidities. By doing so, we were able to test if OSA was an independent risk factor for primary CNS cancers. Nevertheless, the possibility remained that some comorbidities were intermediate variables between OSA and primary CNS cancers.

The comorbidities included obesity (ICD-9-CM codes 278.0, 278.00, 278.01, and 278.02), coronary artery disease (CAD) (ICD-9-CM code 4140), hypertension (HTN) (ICD-9-CM codes 401–405), DM (ICD-9-CM code 250), hyperlipidemia (ICD-9-CM code 272), chronic kidney disease (CKD) (ICD-9-CM codes 585–586), chronic hepatitis (ICD-9-CM codes 070 and 571.4), liver cirrhosis (ICD-9-CM codes 571, 571.2, 571.5, and 571.6), cerebrovascular diseases (CVD) (ICD-9-CM code 438), Parkinson disease (PD) (ICD-9-CM codes 332 and 094.82), and Alzheimer disease (AD) (ICD-9-CM codes 290.4, 294.1, and 331.0). A 2-tail P value of less than 0.05 was considered to indicate statistical significance. We used SAS 9.1 statistical software (SAS Institute, Inc., Cary, NC, USA) to perform the analysis.

3. Results

3.1. Participant characteristics

Table 1 shows the clinical characteristics of both study cohorts. All comorbidities, including obesity, CAD, HTN, DM, dyslipidemia, CKD, chronic hepatitis, liver cirrhosis, CVD, PD and AD were more prevalent in the OSA group than in the comparison group.

3.2. Incidence of primary CNS cancers

During the 10-year follow-up period, we identified 38 cases (0.16%) of primary CNS cancer (brain [n = 32] and spinal cord [n = 6]) in the OSA group and 85 cases (0.12%) of CNS cancer (brain [n = 65] and spinal cord [n = 20]) in the comparison group (Table 1).

Table 1
Clinical characteristics of both study cohorts.

	Sleep apnea group (n = 23,055)	Comparison group (n = 69,165)	P values
Mean age ± SD, y	37.6 ± 8.2	37.6 ± 8.2	0.85
Gender (M:W), %	66.8:33.2	66.8:33.2	>0.99
Obesity, %	4.1	0.1	<0.001
CAD, %	2.1	0.3	<0.001
HTN, %	17.9	3.9	<0.001
DM, %	8.1	2.4	<0.001
Dyslipidemia, %	15.3	2.6	<0.001
CKD, %	1.2	0.3	<0.001
Chronic hepatitis, %	23.6	5.1	<0.001
Liver cirrhosis, %	2.2	0.5	<0.001
CVD, %	3.3	0.6	<0.001
Parkinson disease, %	0.3	0.04	<0.001
Alzheimer disease, %	0.1	0.02	<0.001
Incidence density of CNS cancers (/10,000 individual-years)			
Brain+spine	2.14	1.28	
Brain	1.80	0.98	
Spine	0.34	0.30	

Abbreviations: SD, standard deviation; y, years; M, men; W, women; CAD, coronary artery disease; HTN, hypertension; DM, diabetes mellitus; CKD, chronic kidney disease; CVD, cerebrovascular diseases; CNS, central nervous system.

Incidence density per 10,000 individuals-years was 2.14 for CNS cancers, 1.80 for brain cancers, and 0.34 for spinal cord cancers in the OSA group. Overall, the incidence density was higher in the OSA group than in the comparison group for primary CNS cancers (Table 1), and the attributed risk was 25.4% for primary CNS cancers. Table 2 shows the adjusted hazard ratios (HR) and 95% confidence intervals (CI) for primary CNS cancers associated with OSA identified by Cox regression analysis. Participants with OSA had significantly higher risk for developing primary CNS cancers (adjusted HR, 1.54 [95% CI, 1.01–2.37]; $P = 0.046$) after adjusting for age, gender, obesity, CAD, HTN, DM, dyslipidemia, CKD, chronic hepatitis, liver cirrhosis, CVD, PD and AD. The cumulative HR for primary CNS cancers in the OSA and comparison groups is shown in Fig. 1.

Table 3 shows the adjusted HR and 95% CI of primary brain or spinal cord cancers associated with OSA estimated by Cox regression analysis. Patients with OSA had significantly higher risk for primary brain cancers (adjusted HR, 1.71 [95% CI, 1.06–2.75]; $P = 0.027$) but not for spinal cord cancer (adjusted HR, 1.04 [CI, 0.38–2.80]; $P = 0.942$), after adjusting for other variables. The cumulative HR for developing primary brain or spinal cord cancers in the OSA and comparison groups are shown in Figs. 2 and 3, respectively. In the OSA subgroup analysis, the subgroup with insomnia and OSA (adjusted HR, 2.20 [95% CI, 1.39–3.49]; $P = 0.001$) but not the subgroup with hypersomnia and OSA (adjusted HR, 1.24 [95% CI, 0.70–2.20]; $P = 0.445$) had significantly higher risk for primary CNS cancers than the comparison group. The cumulative hazards for developing primary CNS cancers in the insomnia with OSA subgroup, hypersomnia with OSA subgroup, and comparison group are shown in Fig. 4.

Furthermore, the risk for primary CNS cancers was significantly higher in the OSA group without surgical treatment (adjusted HR, 1.83 [95% CI, 1.23–2.74]; $P = 0.003$) subgroup than in the comparison group, but the HR similar between the OSA with surgical treatment subgroup and the comparison group (adjusted HR, 0.98 [95% CI, 0.31–3.09]; $P = 0.967$). The cumulative hazards for developing primary CNS cancers in the OSA without surgical treatment subgroup, OSA with surgical treatment subgroup, and the comparison group are shown in Fig. 5.

Table 2
Adjusted hazard ratios (with 95% confidence intervals) for central nervous system cancers associated with sleep apnea syndrome identified by Cox regression analysis.

Variables	Adjusted HR	95% CI	*P* value
Sleep apnea	1.54	1.01–2.37	0.046
Age (y)	1.05	1.03–1.08	<0.001
Gender (men vs women)	0.73	0.51–1.05	0.094
Obesity	Dropped		
CAD	0.62	0.08–4.50	0.632
HTN	1.25	0.70–2.25	0.452
DM	0.93	0.41–2.11	0.866
Dyslipidemia	1.40	0.72–2.73	0.316
CKD	Dropped		0.86
Chronic hepatitis	1.20	0.68–2.12	0.529
Liver cirrhosis	1.26	0.30–5.23	0.755
CVD	2.26	0.89–5.76	0.086
Parkinson disease	Dropped		
Alzheimer disease	Dropped		

Abbreviations: HR, hazards ratio; CI, confidence interval; CAD, coronary artery disease; HTN, hypertension; DM, diabetes mellitus; CKD, chronic kidney disease; CVD, cerebrovascular diseases.

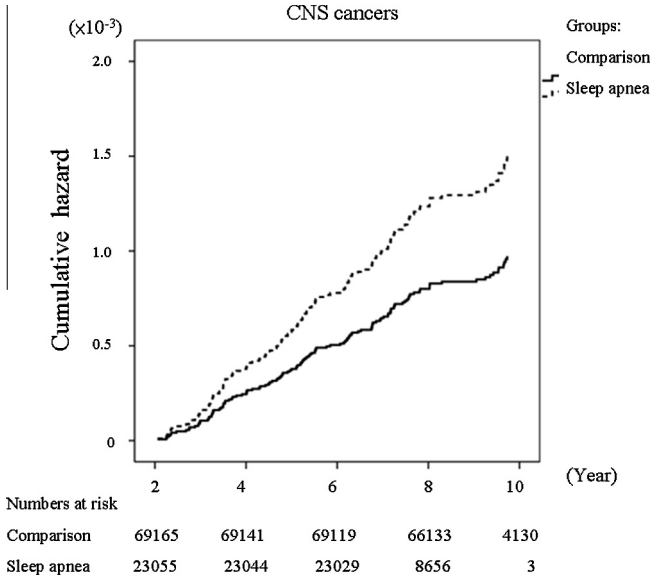

Fig. 1. The cumulative hazard of central nervous system (CNS) cancers. The hazard of CNS cancers was higher in the obstructive sleep apnea group than in the comparison group.

4. Discussion

Our cohort study observed the medical claims database of Taiwan's NHI program as the data source, and showed that OSA may increase the risk or precede the development of primary CNS cancers. Nevertheless, surgical treatment may reduce the risk for primary CNS cancers. This clinical observation supports experimental findings showing that hypoxia can lead to tumor formation including formation of primary CNS tumors [6–8,14].

To our knowledge only a limited number of risk factors have been associated with primary CNS or brain cancers to date. In particular, head trauma or seizures [15], sugar intake, occupational exposure to carbon tetrachloride [16], exposure to lead [17] and alcohol consumption [18] were reported to increase the risk for glioblastoma; and consumption of caffeinated beverages including coffee and tea were reported to possibly reduce the risk for adult glioma [19,20]. In our study, we suggested that OSA, especially with insomnia, may be a new risk factor for primary CNS cancers.

Unlike benign brain tumors, malignant brain tumors often grow rapidly, so the possibility of reverse causation is low. To avoid the possibility of reverse causation, participants with a history of CNS cancers diagnosed before the index date and all cancer cases within 2 years of the index date were excluded from our data analysis. After these exclusions our analysis found that OSA increased the risk for CNS cancers, though reverse causation might still be present. Thus we suggest that OSA may play two roles based on our results and previous reports: one as an early indicator of brain tumors and the other as an initiator of cancer development.

Although most sleep problems in children develop after the start of treatment for CNS cancers, some sleep problems present before CNS cancers are diagnosed [21]. Our results showed a possible cause-effect relationship between OSA and CNS cancers. In addition, sleep-disordered breathing may increase the incidence of all cancers, especially in men and patients younger than the age of 65 years according to a large multicenter Spanish cohort study [13]; it also increased the total cancer mortality after adjusting for age, sex, body mass index and smoking according to the Wisconsin Sleep Cohort Study [22]. Taiwanese patients with non-apnea sleep disorders (ICD-9-CM codes 780.5 and 307.4) have a higher risk for developing liver cancer and possibly breast cancer [23]. Moreover, postmenopausal breast cancer risk was reported to significantly decline with increasing self-reported hours of sleep among Chinese women in Singapore [12], and long sleepers in the Finnish Twin Cohort were reported to have lower breast cancer risk [11]. Our study also found that the interaction of sleep duration

Table 3
Adjusted hazard ratios (with 95% confidence intervals) for brain or spinal cord cancers associated with sleep apnea syndrome identified by Cox regression analysis.

Variables	Brain cancers			Spinal cord cancers		
	Adjusted HR	95% CI	*P* value	Adjusted HR	95% CI	*P* value
Sleep apnea	1.71	1.06–2.75	0.027	1.03	0.38–2.80	0.942
Age (y)	1.05	1.02–1.08	<0.001	1.04	0.99–1.10	0.088
Gender (men vs women)	0.78	0.52–1.18	0.236	0.59	0.27–1.28	0.181
Obesity	Dropped			Dropped		
CAD	0.71	0.10–5.23	0.736	Dropped		
HTN	1.31	0.69–2.47	0.415	0.99	0.21–4.63	0.987
DM	1.13	0.49–2.61	0.767	Dropped		
Dyslipidemia	1.59	0.78–3.23	0.200	0.62	0.08–5.13	0.659
CKD	Dropped			Dropped		
Chronic hepatitis	1.02	0.53–1.95	0.953	2.32	0.74–7.30	0.150
Liver cirrhosis	1.57	0.37–6.62	0.583	Dropped		
CVD	2.08	0.73–5.90	0.169	3.34	0.42–26.91	0.257
Parkinson disease	Dropped			Dropped		
Alzheimer disease	Dropped			Dropped		

Abbreviations: HR, hazards ratio; CI, confidence interval; y, years; CAD, coronary artery disease; HTN, hypertension; DM, diabetes mellitus; CKD, chronic kidney disease; CVD, cerebrovascular diseases.

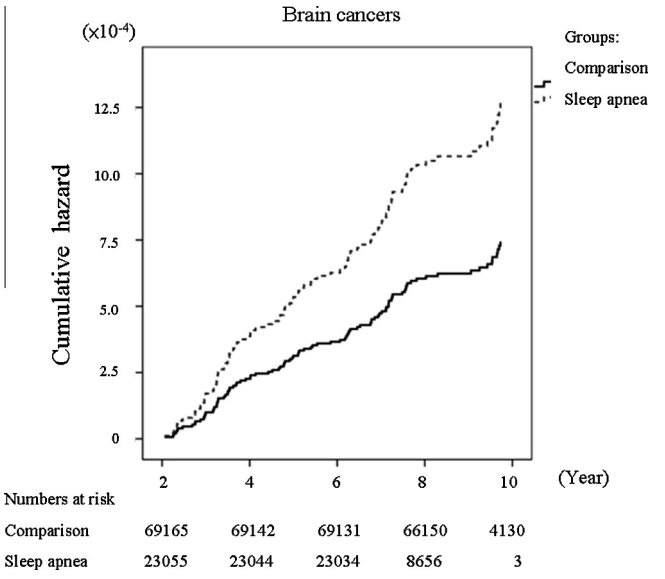

Fig. 2. The cumulative hazard of brain cancers. The cumulative hazard of brain cancers was significantly higher in the obstructive sleep apnea group than in the comparison group.

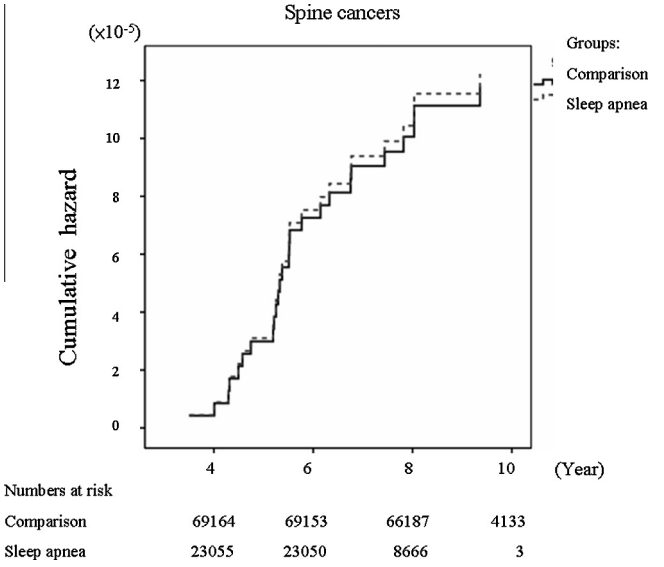

Fig. 3. The cumulative hazard of spinal cord cancers. The cumulative hazard of spinal cord cancers was not significantly higher in the obstructive sleep apnea group than in the comparison group.

with OSA impacts the risk for primary CNS cancers. Overall, sleep disorders with apnea or nonapnea may increase the risk for various cancers in humans.

Poor sleep enhances proinflammatory cytokine production and may induce immunosuppression [24], which plays an important role in the initiation of cancer in postorgan transplant patients [25] and patients with human immunodeficiency virus [26]. Hypoxia also plays a role in glioma tumorigenesis. The progression of a low-grade astrocytoma to a glioblastoma multiforme may be mediated by hypoxia-induced phenotypic changes and subsequent clonal selection of cells [7,8]. The hypoxic microenvironment maintains glioblastoma stem cells and promotes reprogramming towards a cancer stem cell phenotype [14]. In addition, several hypoxia-responsive genes are reported to be associated with patient survival [8]. Hypoxia-induced autophagy promotes tumor cell survival and adaptation to antiangiogenic treatment in glioblastoma [27]. These experimental findings correlate well with clinical observations.

Although the efficacy of nasal surgery in treating OSA is limited [28], the overall success rate of treating severe OSA with uvu-

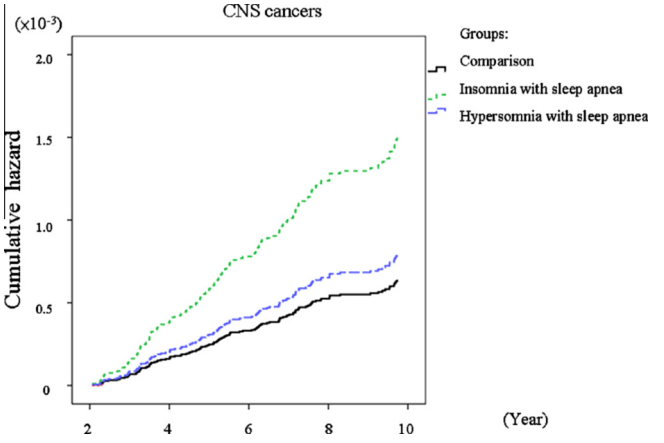

Fig. 4. The cumulative hazard of central nervous system (CNS) cancers in the insomnia with obstructive sleep (OSA) apnea subgroup, hypersomnia with OSA subgroup, and the comparison group. The insomnia with OSA subgroup but not the hypersomnia with sleep apnea subgroup had a significantly higher cumulative hazard for CNS cancers than the comparison group.

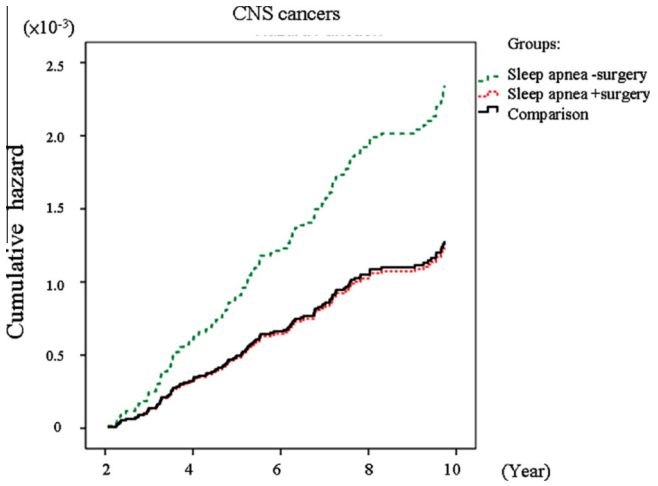

Fig. 5. The cumulative hazard for central nervous system (CNS) cancers in the obstructive sleep apnea (OSA) without surgical treatment subgroup, OSA with surgical treatment subgroup, and the comparison group. The sleep apnea without surgical treatment subgroup but not the OSA with surgical treatment subgroup had a significantly higher cumulative hazard for CNS cancers than the comparison group.

lopharyngopalatoplasty plus genioglossal advancement or tongue base suspension was found to be between 52.3% and 78% [29,30]. Furthermore, in comparison to no treatment, adenotonsillectomy for OSA was found to reduce symptoms of behavioral disorders and increase the quality of life and polysomnographic findings in school-aged children [31]. Our cohort study also demonstrated that surgical treatment may reduce the risk for primary CNS cancers. Phillips et al. [32] reported that mandibular advancement device or continuous positive airway pressure (CPAP) therapy for one month can reduce apnea-hypopnea index events per hour and sleepiness, and increase driving simulator performance and disease-specific quality of life in participants with moderate to severe OSA. According to the results, CPAP therapy did not significantly reduce the incidence of hypertension or cardiovascular events in patients with OSA without daytime sleepiness [33], though a small decrease in blood pressure was found after one year of CPAP therapy in nonsleepy hypertensive patients with OSA [34]. However, no mandibular advancement device and CPAP data were available in our database.

In our study, data were obtained from the Taiwanese NHI program (Taiwan's Health Insurance System) covering more than 96% of the population and maintaining contracts with 97% of hospitals and clinics since the end of 1996. Consequently, the results of the study can be generalized. One major limitation was that it was impossible to adjust for the body mass index (BMI), lifestyle and behavior of the patient in our study due to the lack of data. Although obesity is now adjusted for, the lack of BMI data is still a limitation as BMI is much more informative and the incidence of cancer and apnea is even higher in overweight individuals. Uncontrolled confounding factors such as excessive alcohol use also may be responsible for OSA and CNS cancer associations. However, we excluded patients with other respiratory abnormalities (ICD-9-CM code 786.09) or apnea (ICD-9-CM code 786.03) in both groups. Thus our results could not be confounded by the presence of chronic obstructive pulmonary disease or obesity hypoventilation.

PSG was less available and less frequently performed in Taiwan in early 2000. Therefore, most cases of OSA in our study were diagnosed on the basis of clinical symptoms (i.e., persistent snoring and apnea with witness). Besides, the apnea severity data were not available in the database. Because the positive predictive rate of snoring in detecting OSA was 54% [35] or 66.2% (unpublished data of my hospital), we surmised that the positive predicted rate of snoring plus apnea with witness should be higher than that of snoring only, though the exact value was never reported. We also could not rule out that all participants in the control group did not have OSA (false negative), and that some participants in the OSA group did have OSA (false positive). Considering these two informational misclassifications, we expected that actual HRs would be higher than the calculated HRs.

5. Conclusion

The results of our retrospective cohort study suggest that OSA can precede or increase the risk for primary malignant CNS cancer development. Moreover, surgical treatment may reduce the risk for primary CNS cancers in patients with OSA. We suggest that OSA should be more aggressively treated and clinicians should pay more attention to the OSA-related sequelae.

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Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2013.11.782.

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